Ergonovine-Provoked Esophageal Spasm During Coronary Angiography

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In many patients with chest pain of esophageal origin, findings are normal on routine esophageal manometry and dysmotility develops only upon provocation with ergonovine maleate. Unfortunately, ergonovine may induce myocardial ischemia in patients in whom coronary artery spasm did not occur during previous provocative testing in a cardiac laboratory—limiting its clinical usefulness. We have recorded esophageal pressure simultaneously with ergonovine infusion during angiography in ten patients without significant arterial stenoses. In two patients their usual chest pain developed associated with esophageal spasm and without changes in coronary vessels. Simultaneous performance of angiography and manometry enhanced the diagnostic yield of provocative testing by showing esophageal motility changes. This method may detect significant changes in the esophageal motility, is easy to carry out and does not interfere with angiography. It maximizes the information gained from a single provocative test and avoids the risk of ergonovine infusion outside of a cardiac laboratory.

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The cause of chest pain in patients with angiographically normal coronary arteries is often enigmatic despite an array of sophisticated diagnostic studies. Chest pain clinically indistinguishable from angina pectoris can arise as a result of esophageal spasm.[1-4] Unfortunately, motility disorders of the esophagus may go unrecognized because the characteristic signs of spasm may not occur at the time of esophageal manometry.[5,6] Hence, a provocation test for esophageal spasm is an attractive concept.

Ergonovine maleate, an adrenergic agonist, is a nonspecific stimulator of smooth muscle contraction and has been used as a provocative agent during coronary angiography to identify focal coronary spasm in patients who have chest pain.[7-9] In up to a third of patients with ergonovine-provoked chest pain there are no changes in simultaneous electrocardiograms and coronary angiograms.[10] Speculation has recently focused on the esophagus as a source of pain in some of these patients.[2,11]

Several investigators have administered ergonovine during esophageal manometric studies to determine whether or not ergonovine can provoke esophageal motility changes and chest pain in patients with normal coronary vessels.[5,6,11-13] Provocation testing was carried out in a manometry laboratory after patients had had no significant coronary spasm during a previous ergonovine infusion. These studies show that chest pain and esophageal motility changes may be provoked by ergonovine in some patients, providing valuable diagnostic information, but not without some risk. Ergonovine infusion may induce myocardial ischemia in patients who failed to demonstrate coronary artery spasm during previous provocation tests in a cardiac laboratory.[5] Coronary vasospasm and serious ventricular arrhythmias induced by ergonovine may be refractory to sublingual or intravenous administration of nitroglycerin.[14,15] Deaths have been reported during use in a cardiac laboratory despite all appropriate precautions. We agree with others[5,6,13] that this risk precludes routine diagnostic provocation testing in a manometry laboratory.

Therefore, we propose recording esophageal pressure

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TABLE 1.—*Clinical Characteristics and Evaluation of Patients Before Ergonovine Study*

Patient, Age, Sex	Symptoms		Cardiac Evaluation				Gastrointestinal Evaluation Diagnostic Studies
			Electrocardiogram				
	Chest Pain	Gastrointestinal History	Resting	Exercise	Other Studies	Treatment	
1 51 ♀ ...	2 months of intermittent pain, palpitation, dizziness	None	Premature ventricular contractions	No ischemia	Electrophysiology (−)	Quinidine; propranolol hydrochloride	None
2 28 ♀ ...	**18 months of daily nocturnal pain**	**None**	**Normal**	**No ischemia Limited by dyspnea**	**Coronary angiogram 4/81 (−); Holter monitoring (−)**	**Nadolol; nitrates**	**None**
3 58 ♀ ...	3 months of frequent pain every day at rest	Heartburn; occasional proximal dysphagia	Normal	ST-T depression without chest pain	Two hospital admissions for chest pain	Nitrates; metoprolol tartrate	Upper gastrointestinal series (UGI): Esophageal reflux; abdominal ultrasonogram (−)
4 44 ♀ ...	**36 months of twice-a-week rest pain; no relief with nitrates**	**Heartburn; dysphagia to solids**	**Normal**	**No ischemia; limited by dizziness**	**Cardiac echo (−)**	**Propranolol; nitrates**	**UGI (−)**
5 53 ♀ ...	7 months of nocturnal pain; minimal relief with nitrates	Minor heartburn	Nonspecific ST-T abnormalities	No ischemia	Holter monitoring (−); cardiac echogram(−); cold pressor test (−)	Nitrates; cimetidine	UGI (−); cimetidine trial: no improvement
6 47 ♀ ...	**18 months of twice-a-week rest pain**	**Prior duodenal ulcer**	**Right bundle branch block**	**Incomplete: limited by weakness**	**None**	**None**	**None**
7 41 ♂ ...	36 months of rest pain 8 times per day; some relief with nitrates	Minor heartburn	Normal	Thallium study: possible apical ischemia	7 hospital admissions for chest pain; cardiac echogram (−); coronary angiogram 8/80 (−);	Nitrates; nifedipine	None
8 64 ♀ ...	**20 years of daily rest pain of up to 3 hours' duration**	**Prior ulcer and gastric operation; rare dysphagia**	**Right bundle branch block**	**No ischemia**	**6 hospital admissions for chest pain; coronary angiogram 1973 (−)**	**Nitrates**	**None**
9 43 ♀ ...	36 months of daily pain with exertion or stress; some relief with nitrates	None	Normal	No ischemia	Cardiac echogram: mitral valve prolapse	Nitrates; metoprolol	None
10 43 ♀ ...	**15 years of daily pain in supine position lasting up to 4 hours**	**Dysphagia; occasional nausea and vomiting**	**Normal**	**Thallium study: equivocal**	**4 hospital admissions for chest pain**	**Antacids**	**Esophagogram: normal; endoscopy: normal; esophageal manometry: nonspecific motility disorder**

(−) = negative/no abnormalities

TABLE 2.—*Results of Coronary Angiography and Ergonovine Infusion*

Patient	Baseline Coronary Angiogram	Ergonovine Dosage mg	During Ergonovine Infusion: Symptoms	Coronary Angiogram	Esophageal Motility
1	Normal	0.35	None	No change	Few simultaneous contractions
2	Normal	0.50	None	Focal spasm of RCA	No change
3	25% LAD lesion	0.15	Chest pain	No change	Simultaneous repetitive low-amplitude contractions
4	Normal	0.2	Chest pain	No change	High-amplitude simultaneous contractions
5	30% LAD lesion	0.3	None	Diffuse spasm RCA; focal spasm LAD	No change
6	Normal	0.4	None	Slight diffuse narrowing (40%)	No change
7	30% RCA lesion; 25% LAD lesion	0.5	Mild nausea; light-headed	No change	No change
8	Normal	0.4	None	Slight diffuse narrowing (40%)	No change
9	Normal	0.4	Chest pain; nausea	No change	No change
10	Normal	0.3	Mild chest pressure	No change	Few simultaneous contractions; no change from baseline

LAD = left anterior descending artery; RCA = right coronary artery.

TABLE 3.—*Summary of Results of Ergonovine Infusion*

Symptoms	Number of Patients	Coronary Artery Spasm	Esophageal Spasm	No Spasm of Coronary Arteries or Esophagus
Chest pain	3	0	2	1
No chest pain .	7	2	0	5

during coronary angiography with ergonovine provocation. Our goals are to enhance the diagnostic yield of coronary angiography, to carry out provocation testing with ergonovine under the safest possible conditions and to avoid the risk of ergonovine infusion outside of a cardiac laboratory.

Patients and Methods

Our study comprised 12 patients with chest pain or arrhythmias, or both. All were scheduled to undergo coronary angiography and receive ergonovine if no fixed coronary artery lesions were detected. Two patients had significant coronary stenoses and did not receive ergonovine. The remaining ten patients had long histories of chest pain resembling angina pectoris but had some atypical features. Age, sex and previous study results are listed in Table 1.

The patients gave written informed consent (study approved by The Oregon Health Sciences University Committee on Human Research, 11/18/81). Nitrates, calcium channel blocking agents and β-blocking agents were discontinued at least 24 hours before the study. After an overnight fast a three-channel continuous perfusion motility catheter was introduced through the nose without sedation or local anesthesia. The catheter was passed into the stomach and the patient transferred to the angiography suite. Channels at the tip of the catheter and 5 cm back of the tip were perfused with water via Harvard perfusion pumps at a rate of 0.7 ml per minute. Esophageal intraluminal pressure was transmitted from the catheter assembly to two external transducers (Statham, P-23Db) and their output recorded on a multichannel recording system. The catheter was withdrawn into the esophagus so that the lowest channel was 3 to 5 cm above the lower esophageal sphincter and the proximal channel at 8 to 10 cm above the lower sphincter. Intraluminal pressures were recorded from these two sites in the esophageal body simultaneously.

Standard coronary angiography was carried out. If no significant fixed coronary lesions were seen, the patient received intravenous infusions of ergonovine maleate while the angiographic catheter remained in the aorta. Infusions of 0.05 mg of ergonovine were given at two-minute intervals during continuous intra-aortic blood pressure and six-lead electrocardiographic monitoring. The patients were asked at frequent intervals whether they had their typical chest pain or other symptoms. Infusions were terminated if severe chest pain occurred, if systolic blood pressure rose more than 40 mm of mercury, if ischemic electrocardiographic changes occurred or when a maximal dose of 0.005 mg per kg of body weight was administered. Left and right coronary artery angiography was repeated at the end point. Coronary artery spasm was defined as a new stenosis with 70% reduction in luminal diameter as compared to the preergonovine angiogram. Nitroglycerin was administered sublingually at the end of each study.

Tracings of esophageal motility were continuously observed during and after ergonovine infusions. Changes from baseline motility were noted and correlation with chest pain symptoms was possible. The motility catheter was removed immediately after the angiography was completed. Patients who experienced ergonovine-induced chest pain and no coronary spasm were invited to have a complete esophageal manometry examination in the gastrointestinal laboratory. Esophageal spasm was

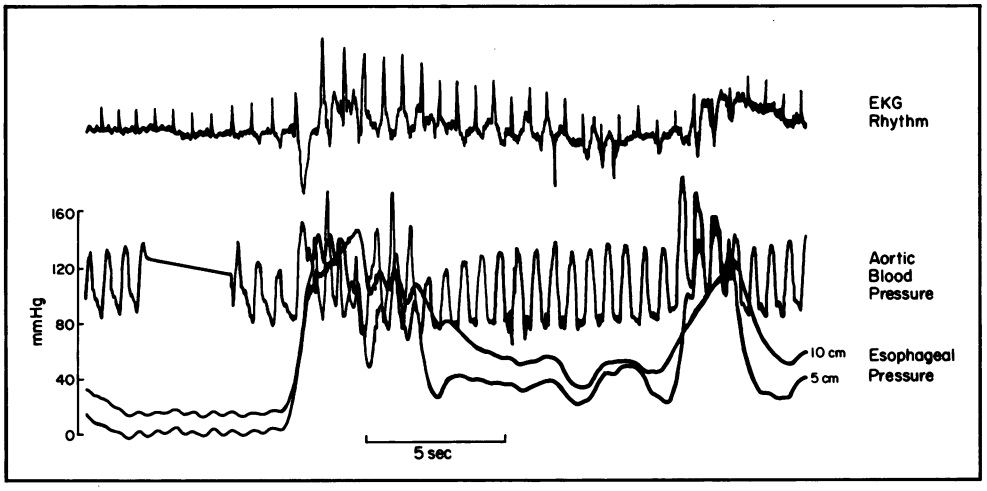

Figure 1.—Electrocardiographic (EKG), aortic blood pressure and esophageal motility tracings carried out during ergonovine infusion (patient 4). The esophageal pressure is measured simultaneously from two points in the esophageal body, 5 and 10 cm above the lower sphincter. The appearance of high-amplitude, simultaneous and peristaltic esophageal contractions coincided with the onset of chest pain. mmHg = mm of mercury

defined as the presence of (1) frequent simultaneous or repetitive contractions in the proximal and distal esophagus or (2) the presence of prolonged (greater than seven seconds) or high-amplitude (greater than 120 mm of mercury) contractions (or both 1 and 2). Normal amplitude values for our manometry laboratory are 60 to 100 mm of mercury.

Results

Two of the twelve patients evaluated were found to have significant obstructive lesions of the coronary arteries and did not receive ergonovine. The ten patients without significant coronary artery stenosis who received ergonovine are the subjects of the study (Table 1). Three patients experienced their usual chest pain during the ergonovine infusion (Tables 2 and 3). Changes in blood pressure or in findings on a 12-lead electrocardiogram did not occur in these cases. Repeat coronary angiograms during chest pain failed to detect significant coronary artery spasm in these patients. However, two of the patients had pronounced changes in esophageal motility, detected on continuous esophageal pressure tracings at the time of chest pain.

Patient 3, a 58-year-old woman, had been admitted to hospital twice in the previous three months with dull substernal chest pain occurring up to five times per day at rest and with exertion or anxiety. An exercise stress test had shown mild ST and T-wave changes consistent with myocardial ischemia. Nitrates were ineffective. She also gave a history of intermittent heartburn and occasional cervical dysphagia associated with anxiety and gulping of food. An upper gastrointestinal x-ray series showed no abnormalities. Chest pain during the ergonovine infusion was associated with the onset of repetitive, normal amplitude, simultaneous contractions of the esophagus. She was relieved that the angiographic study was normal and declined further evaluation with standard esophageal manometry.

Patient 4, a 41-year-old woman, had a 3½-year history of intermittent upper chest, neck and left arm pain usually occurring at rest, with no known precipitating causes. She had been evaluated in emergency rooms on two occasions to rule out myocardial infarction. An upper gastrointestinal x-ray series before angiography showed no abnormalities. At least ten swallows were observed before ergonovine infusion that were all peristaltic, with maximal amplitudes of 70 to 96 mm of mercury. During the ergonovine infusion, simultaneous and peristaltic high-amplitude contractions of the esophageal body (greater than 120 mm of mercury) developed, associated with the onset of squeezing chest pain (Figure 1). Coronary angiogram findings remained normal despite continuous chest pain. Diminution in pain occurred with sublingual nitroglycerin and her symptoms resolved spontaneously within 10 to 15 minutes of the last ergonovine injection. Following the positive ergonovine provocation test she consented to a standard manometric examination. At this time chest pain was precipitated by drinking ice water. Manometric findings included a hypertensive lower esophageal sphincter (50 mm of mercury) and high-amplitude (150 mm of mercury) peristaltic contractions associated with chest pain (Figure 2). In retrospect, she acknowledged that her symptoms frequently followed the ingestion of cold liquids. Over a 12-month follow-up period she has remained asymptomatic without medication by avoiding cold liquids.

A third patient (number 9) had chest pain after 0.4 mg of ergonovine. No changes in coronary arteries or esophageal motility were noted and the cause of her chest pain remains obscure.

In two patients (numbers 2 and 5) coronary spasm (focal stenosis greater than 70%) developed during ergonovine infusion. Neither patient complained of chest pain or had electrocardiographic changes. Arterial spasm resolved promptly with sublingual nitroglycerin. In no patient did esophageal spasm occur without associated chest pain. One patient (number 10) had a history of symptoms suggestive of esophageal disease including viselike chest pain in the supine position, relieved by sitting upright, and cervical-esophageal dysphagia, nausea and vomiting. Results of previous endoscopy were normal. Routine esophageal manometry showed normal lower esophageal sphincter pressure (27 mm of mercury) and function, and normal peristalsis in the esophageal body with few simultaneous

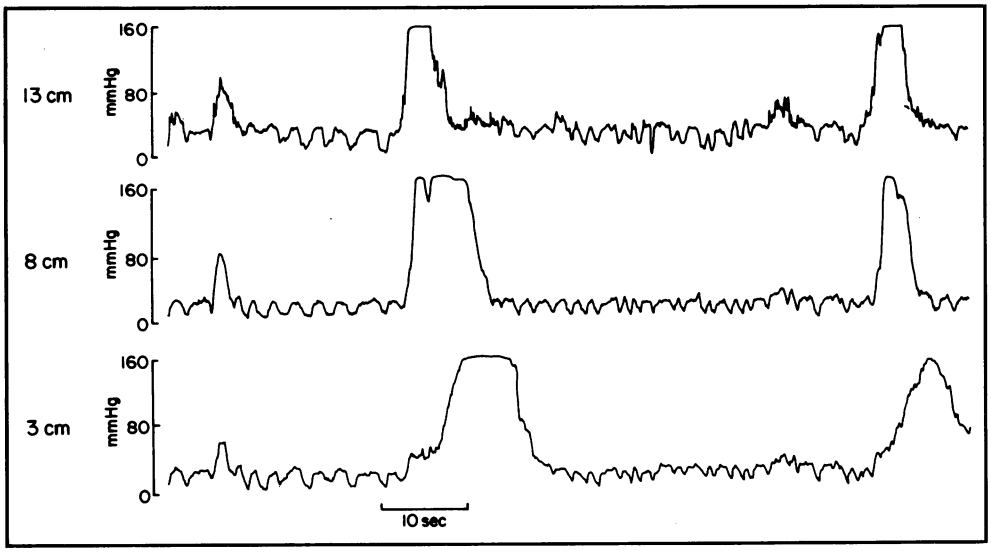

Figure 2.—Esophageal motility tracing from patient 4 with simultaneous recordings at 3, 8 and 13 cm above the lower esophageal sphincter. High-amplitude (greater than 160 mm of mercury), long duration (greater than 7 sec), peristaltic contractions were observed during an episode of chest pain. mmHg = mm of mercury

contractions. A Bernstein test was negative. Before ergonovine infusion, her baseline manometric tracings showed simultaneous contractions associated with 25% of swallows. She had minor left chest discomfort during ergonovine infusion, which resolved as she received more ergonovine. No significant changes in coronary vessels or esophageal motility were observed after 0.3 mg of ergonovine was administered. Although mild esophageal dysmotility was observed in this patient, no relationship with chest pain could be established.

No definite diagnosis was made in six of ten patients who received ergonovine. The mild diffuse coronary spasm in patients number 6 and 8 was not significant. No other adverse effects of ergonovine were observed in our patients.

Discussion

Ergonovine-induced esophageal spasm was shown to be the cause of chest pain in two of ten patients during simultaneous coronary arteriography and esophageal manometry. Although ergonovine-induced chest pain is used as an indication of coronary artery spasm, manometric signs of esophageal spasm or dysmotility have been seen in some patients.[5,6,11-13] Adrenergic stimulation of esophageal dysmotility with ergonovine may or may not be analogous to in vivo esophageal spasm development. Therefore, the value of provocation testing is limited to patients in whom typical chest pain develops coincident with esophageal motility changes. Interpretation of the importance of motility changes without symptoms should be cautious.

Ergonovine provocation testing in patients with suspected esophageal dysmotility is associated with some risk of myocardial ischemia. Therefore, in each of the previously reported investigations, ergonovine was administered in the gastrointestinal laboratory after previous infusion during coronary angiography. The absence of coronary artery spasm during properly performed ergonovine provocation in a cardiac catheterization laboratory is probably predictive that such spasm is unlikely to occur during a second provocation test. However, the serious consequences of refractory ergonovine-induced spasm have been documented[14-16] and would be most disconcerting if encountered in a manometry suite. Buxton and co-workers[14] have noted that some cases of severe spasm may be responsive only to intracoronary nitroglycerin. We conclude with others[5] that ergonovine infusion should usually be carried out in an angiography suite where intracoronary medication can be administered.

For patients who have ergonovine-induced chest pain without changes in electrocardiographic or coronary angiographic findings, simultaneous esophageal manometry can provide important diagnostic information. Our results show the feasibility of carrying out simultaneous angiography and manometry in patients receiving ergonovine. Patient discomfort from the presence of a nasoesophageal tube was minimal. Calibration and recording of esophageal pressures in the cardiac laboratory presented no special problems. There was no interruption of, or interference with, the angiographic procedure due to the manometric recording.

Our cases illustrate the emotional and financial burdens of undiagnosed chest pain. Ockene and associates[17] have followed the functional state of similar patients with angiographically normal coronary arteries. Although their long-term medical prognosis was excellent, nearly half of the patients remained limited by chest pain and unable to work and believed that they indeed had heart disease. Both of our patients with abnormal findings on esophageal studies had atypical chest pain that had defied diagnosis despite several hospital admissions and diagnostic cardiovascular tests. Results of routine coronary angiography were normal and provided valuable negative information. Ergonovine provocation failed to induce coronary spasm though chest pain was precipitated. Hence, no diagnostic information would have been gained from angiography without the simultaneous esophageal studies. Unfortunately, no definite diagnosis was made in eight other patients who

received ergonovine, though in two patients focal coronary artery spasm developed without concomitant chest pain and in one patient mild esophageal dysmotility was noted.

In conclusion, simultaneous angiography and esophageal manometry during ergonovine provocation testing is easy to carry out and may enhance the diagnostic yield of the procedure. This technique avoids the risk of ergonovine infusion outside of a cardiac laboratory. We recommend the application of this technique in all patients who are candidates for ergonovine provocation testing during coronary angiography.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Endothelial Cell Counts

QUESTION:

Are endothelial cell counts performed by ophthalmologists medically necessary?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, specular endothelial photomicroscopy with endothelial cell counting is considered established medical practice. In selected cases where endothelial disease is suspected or when a patient has had a previous ocular surgical procedure or significant ocular trauma, preoperative endothelial cell counting is helpful in determining if an operation is indicated and, if so, the most appropriate surgical procedure.

The ophthalmic community agrees that endothelial cell photography is a useful procedure which is safe, enjoys wide clinical acceptability as a highly useful measure of corneal health, is highly useful in identifying those patients who would be at a greater risk for serious ocular disease with certain ocular procedures and is effective in differentiating among several important disease processes.